

VIEWPOINT



Should We Do an Individual Management of Septic Shock in Neurocritically Ill Patients? A Proposal of a Conceptual Algorithm

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Abstract

Septic shock (SS) constitutes a complex and potentially severe entity associated with a high mortality rate worldwide. The neurocritically ill patient represents a vulnerable population with a marked tendency to develop SS. In turn, invasive neuromonitoring devices—such as external ventricular drainage (EVD)—may predispose to intracranial infections, which in some cases may progress to SS. Early goal-directed therapy (EGDT) was initially proposed by Rivers et al. for the management of SS. However, lately its application has been discussed due to its higher hospitalization costs and excessive heterogeneity among patients in the baseline inflammation levels and stage of organ dysfunction. Thus, the strategy for addressing these scenarios more effectively might be an individualized approach. To solve this research question, we proposed a novel conceptual algorithm to approach neurocritically ill patients with SS to improve the DO_2/VO_2 ratio and neurological outcome by optimizing the mean arterial pressure (MAP) and cerebral perfusion pressure (CPP) among other hemodynamic and neurocritical parameters.

Keywords: Septic shock, EGDT, MAP, Resuscitation, CPP

Introduction

The approach to septic shock (SS) might be complex, constituting one of the main causes of morbidity and mortality in neurocritically ill patients worldwide [1]. The incidence of sepsis is particularly high in neurointensive care unit (NCCU) settings, whereas SS occurs less frequently, in approximately around 5–6% of patients [1]. Furthermore, ventilator-associated pneumonia (VAP) remains the leading infectious source of sepsis in patients admitted for severe traumatic brain injury (sTBI), accounting for 20–30% of cases [2, 3]. However, invasive monitoring devices of intracranial pressure (ICP), particularly external ventricular drain (EVD), may constitute another potential source of CNS infections (ventriculitis, meningitis, among others), which in some cases may progress to SS [4]. Although there have been many early goal-directed therapy (EGDT) protocols proposed for the treatment of SS since the study by Rivers et al. [5], until now, no management protocol has been proposed for neurocritical patients. This article succinctly presents an

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original clinical algorithm theoretical to manage resuscitation of neurocritically ill patients under diagnosis of SS.

The Clinical Relevance of EGDT

EGDT, a systematic approach that involves the optimization of preload, afterload, and cardiac contractility to improve the ratio of oxygen delivery to oxygen consumption (DO_2/VO_2), has been used for SS since it was raised by the pioneering study conducted by Rivers et al. in 2002 [2]. This novel algorithm showed a reduction of in-hospital mortality and organ dysfunction. However, subsequent trials could not replicate the clinical benefits that were found in that study [6–8].

In Table 1, we pose the primary randomized controlled trials (RCTs) proposed in medical literature during the last 25 years that carried out EGDT in critically ill patients under the diagnosis of SS. The selection criteria considered were articles published in recognized journals; indexed in databases such as PubMed/MEDLINE, Scopus, and Google Scholar; and written only in the English language. In turn, retrospective studies were excluded due to their inherent risk of bias and limited quality of evidence to conclude clinical findings. In terms of the clinical features considered from each of them, the hemodynamic parameters and assessment conclusions were highlighted in a separate column from Table 1.

Results have shown disparities in different studies in terms of clinical outcomes and mortality [5–10].

Thus, a meta-analysis conducted in 2017 has concluded that they did not find a significant difference in terms of mortality in EGDT without any other clear clinical benefit [11]. However, in a more recent RCT conducted in 2018 in Latin America that used an EGDT approach—optimizing fluid responsiveness, vasopressors, and inodilators—in both groups of patients, a reduction in mortality was found by using a novel objective of resuscitation: capillary refill time (CRT) to assess the peripheral perfusion, thus showing promising results supporting this new target [9]. Additionally, supporting Andromeda-Shock et al. in 2018, a novel recent study published since October 2025, [10], carried out in different continents worldwide (South America, North America, and Europe) has evidenced favorably clinical outcomes in the intervention group, which used a personalized hemodynamic resuscitation protocol targeting capillary refill time (CRT) compared with the group that received the normal standard of care, showing an enhancement of the primary composite outcome, which included: primarily mortality, duration of vital support, and length of stay (LOS) in ICU settings at day 28, primarily due to a shorter duration of organ support (Table 1).

Hence, regardless of the novel findings exhibited [10], the overall clinical data compared with previous trials

found mixed results [5–8]. This fact may be explained due to considerable variations among baseline inflammation levels and stage of organ dysfunction in the studied patients [11, 12]. Thus, the key to achieving a better outcome may lie in the implementation of an individualized management for neurocritical patients, rather than applying a universal strategy to all patients with SS without distinction [13]. Therefore, we propose conceptually that EGDT target neurocritically ill patients, as this is the first approach in the literature to describe this concept (Fig. 1). However, it lacks patient involvement or clinical data, constituting a theoretical framework, for which a prospective study will be presented soon.

Role of CPP Management in SS

Cerebral perfusion pressure (CPP) is considered a surrogate measure for the delivery of nutrients to the cerebral tissue. The latest guidelines for the management of severe traumatic brain injury (sTBI) emphasize maintaining a target fixed threshold of CPP [14]. However, the threshold value should be interpreted in the context of the cerebral autoregulation (CA) status, the ability of the cerebral vasculature to maintain stable CBF despite changes in blood pressure [14]. This recommendation is based on the international consensus proposed by the Seattle International Severe Traumatic Brain Injury Consensus Conference (SIBICC) [13].

The mean arterial pressure (MAP) challenge is a practical method suggested to assess CA. In the event of no changes or a decrease in ICP during the test, the CA is supposed to be preserved, and higher thresholds of CPP, such as >70 mm Hg, could be targeted, thereby preventing both secondary ischemia and hyperemia [14]. However, this approach should not be universally applied to every patient because it has inherent risks of causing or exacerbating intracerebral hemorrhage and congestive heart failure [14, 15]. Instead, it should be used in certain scenarios where patients might benefit from higher MAP thresholds, besides sTBI, as already mentioned [13]. For instance, this might be the case in patients with ischemic stroke after an incomplete reperfusion, defined as Thrombolysis in Cerebral Infarction (TICI) Score of 0–2a. In this population, the risk of hypoperfusion of the penumbra outweighs the risk of reperfusion injury and hemorrhagic transformation [16]. Another case to mention is that of aneurysmal subarachnoid hemorrhage (aSAH). In patients with already secured ruptured aneurysms complicated by vasospasm, the hemodynamic optimization, gradually increasing the MAP until the neurological symptom and/or radiological finding resolve, can be considered [15]. Therefore, during SS in these specific scenarios, aiming for higher MAP thresholds than in patients without neurocritical conditions

Table 1 Randomized controlled trials proposed in the last 25 years have planned different approaches to improve the clinical outcomes of critically ill patients with SS and decrease mortality

Study	Country	Design	No. of patients	Clinical outcomes
Rivers et al. 2001 [5]	USA	Single center, prospective, randomized	263	Lower in-hospital mortality in EGDT group: 30.5% in EGDT group vs. 46.5% in standard therapy group ($P=0.009$) Lower mean APACHE II scores (less severe organ dysfunction) in EGDT group: 13.0 ± 6.3 in EGDT group vs. 15.9 ± 6.4 in standard therapy group ($P < 0.001$)
ARISE, Peake et al. 2009. [7]	Australia	Multicenter, prospective, randomized	1600	Mortality by day 90 showed no significant difference: 18.6% in EGDT group vs. 18.8% in the usual care group ($P=0.90$) Mortality by day 28 showed no significant difference: 14.8% in EGDT group vs. 15.9% in the usual care group ($P=0.53$)
ProCESS, Yealy et al. 2014. [6]	USA	Multicenter, prospective, randomized	1341	In-hospital mortality showed no significant difference: 21% in EGDT group vs. 18.2% in the usual care group ($P=0.83$) Higher rates of renal failure in EGDT group during the first week (statistically significant but clinically small difference): 3.1% in EGDT group vs. 2.8% in usual care group ($P=0.04$)
ProMiSe Mouncey et al. 2015. [8]	England	Multicenter, prospective, randomized	1260	Mortality by day 90 showed no significant difference: 29.5% in EGDT group vs. 29.2% in the usual care group ($P=0.90$) Mortality by day 28 showed no significant difference: 24.8% in EGDT group vs. 24.5% in the usual care group ($P=0.90$)
ANDROMEDA-SHOCK, Hernandez et al. 2018. [9]	Chile and others countries from Latin America	Multicenter, prospective, randomized	420	Mortality by day 28 was lower in EGDT group using normalization of CRT as a goal (not statistically significant): 39.4% in EGDT-CRT group vs. 43.4% in EGDT-lactate group ($P=0.06$) The SOFA score at 72 h was lower in EGDT-CRT group: -1 compared with EGDT-lactate group ($P=0.045$)
ADROMEDA-SHOCK-2, Hernandez et al. 2025. [10]	South America, North America, and Europe	Multicenter, prospective, randomized	1467	Hierarchical Composite Outcome (HCE) of mortality, duration of vital support, and length of stay up to day 28 was superior in the CRT-PHR group: 48.9% in the CRT-PHR group vs. 42.1% in the usual care group ($P=0.04$) Vital support-free days within 28 days* was higher in the CRT-PHR group: 16.5 (11.3) in the CRT-PHR group vs. 15.4 (11.4) in the usual care group ($P=$ not applicable)

* Displayed as mean (SD)

(See figure on next page.)

Fig. 1 Conceptual clinical algorithm proposed for early goal-directed therapy in neurocritically ill patients with septic shock. Abbreviations: ARDS acute respiratory distress syndrome, ASM antiseizure medication, BPS Behavioral Pain Scale, CaO_2 arterial oxygen content, CBF cerebral blood flow, CNS central nervous system, CO cardiac output, CPP cerebral perfusion pressure, CRT capillary refill time, cTn cardiac troponin, CVP central venous pressure, CXR chest x-ray; DO_2 oxygen delivery, EEG electroencephalogram, EVD external ventricular drainage, HR heart rate, ICP intracranial pressure, IH: intracranial hypertension, LUS lung ultrasound, LVOT-VTI left ventricular outflow tract velocity time integral, MAP mean arterial pressure, MCA middle cerebral artery, MTT mean transit time, $PtiO_2$ brain tissue oxygen pressure, RASS Richmond Agitation-Sedation Scale, SS septic shock, $SvJO_2$ jugular venous oxygen saturation, SV stroke volume, TCD transcranial Doppler, TICI Thrombolysis in Cerebral Infarction Score, t_0 time zero, VO_2 oxygen consumption

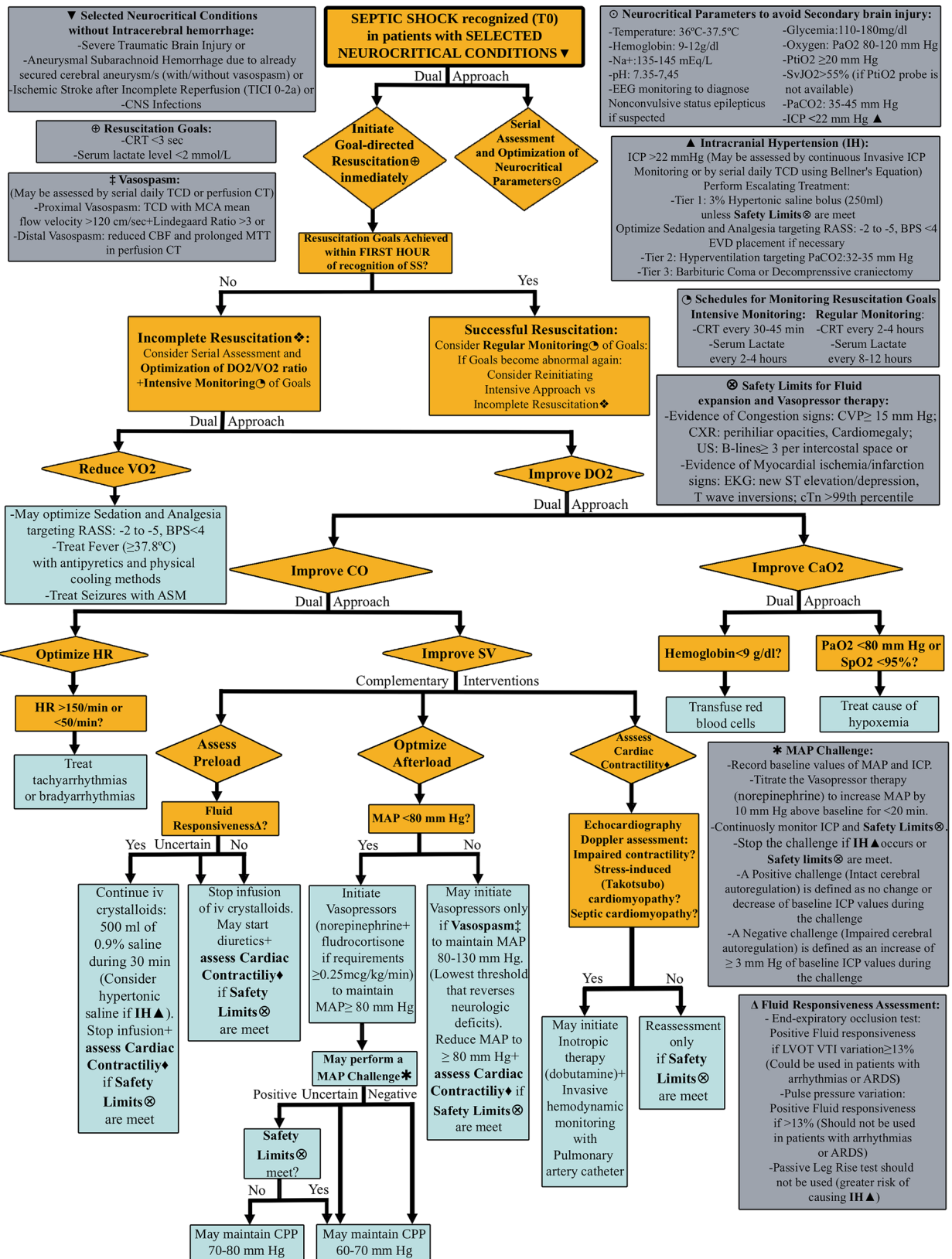


Fig. 1 (See legend on previous page.)

could be essential to achieve adequate CPP management, thereby reducing secondary brain injury due to hypoperfusion.

Clinical Algorithm

Taking into consideration the topics discussed, we have developed a distinctive conceptual algorithm to guide hemodynamic resuscitation in neurocritically ill patients with SS. Hence, this will be the first clinical algorithm proposed for EGDT in neurocritical patients with SS, as shown in Fig. 1. For this purpose, SS has been defined on the basis of SEPSIS-3 consensus [17], such as a persistent hypotension requiring vasopressors to maintain a MAP $\geq$ 65 mm Hg and a lactate concentration greater than 2 mmol/L despite an adequate management of fluids resuscitation.

The protocol aims to improve the DO₂/VO₂ ratio by optimizing each component of the Fick equation [18].

The target population suggested to carry out this algorithm will include patients under diagnosis of SS admitted to the NCCU due to: sTBI, already secured aSAH, CNS infections (e.g., meningitis, ventriculitis), and ischemic strokes after incomplete reperfusion. Additionally, patients may be eligible for the therapeutic algorithm despite presenting with a wide range of baseline conditions, including being sedated or nonsedated and intubated or nonintubated, although they will probably need sedation and mechanical ventilation in the scenario of shock with high requirements of vasopressors. However, patients with intracerebral hemorrhage (ICH) were excluded from this algorithm because MAP augmentation is deleterious for this subgroup of patients.

The early goals of resuscitation may be approached conveniently within the first hour after establishing the diagnosis of SS [13]. Moreover, monitoring these goals may be intensive in the initial stage of resuscitation, mainly through serum lactate measurements every 2–4 h, and CRT assessment every 30–45 min. Once those resuscitation goals are accomplished for the first time, a less frequent schedule of monitoring is suggested. Furthermore, the rest of the hemodynamic parameters may require additional assessment only in the setting of inadequate resuscitation goals [13]. Finally, all other aspects of care, including antimicrobial treatment, may be given on the basis of international guidelines for SS [13–15, 30].

Additionally, in terms of enhancing neuromonitoring, some additional devices depending on artificial intelligence (AI) tools have been proposed in the literature to complement neurological assessment [19]. However, regardless of the “novel” evidence, current data are not enough to support their medical–legal implementation in neurocritically ill patients [20], considering the

risk–benefit and all the limitations that it presents to this vulnerable population. Therefore, this clinical algorithm may not consider using AI tools, thus highlighting that human knowledge and clinical experience remain the pillar of gold-standard care. Consequently, sometimes physicians should still have the capabilities in making individualized decisions, rather than blindly following an algorithm, to avoid harmful decisions that may not be mandatory for all patients [20]. Thus, as we discussed earlier in our hypothesis, the individualized management for patients with SS is critical, and often “standardized” algorithms may not always work for all the possible scenarios. Moreover, we also recognize that not every NCCU may count with the neuromonitoring tools to carry out the “best” management, and recognizing this limitation is a cornerstone in carrying out a versatile approach in terms of hybrid medical settings. Hence, this conceptual algorithm recognizes this limitation and gives a varied set of tools for diverse resource settings.

The novelty of this conceptual algorithm is the addition of neurocritical objectives that may ensure neuroprotection. Mainly, we focused on suggesting objectives for MAP and CPP suitable for each possible clinical scenario. For this reason, we include the MAP challenge to try to assess CA and choose the optimal CPP threshold for each patient. We chose it because we consider that it is the easiest method for this task, as it is available in every possible resource setting. Other methods, such as the transcranial Doppler (TCD)-derived mean velocity autoregulation index (Mx) or the pressure reactivity index (PRx) surrogate, might not be available everywhere because of a lack of devices or trained physicians. To avoid harmful complications of volume expansion or vasopressors, we added safety limits to stop these therapies in case of high risk of pulmonary edema or myocardial ischemia.

Additionally, we integrated target neurocritical parameters to attempt to prevent secondary brain insults [21–23]. In addition, we incorporated imaging monitoring, aiming to identify vasospasm, a complication of ruptured cerebral aneurysm [15], as well as elevated ICP. This last paramount parameter may be assessed using invasive monitoring or TCD, applying the Bellner’s equation [24], particularly in settings with scarce resources. In addition, we added suggestions to guide escalating treatment vs. intracranial hypertension (IH) depending on the volume status on the basis of international consensus [13].

This article presents only a piece of the theoretical framework of our proposed conceptual algorithm. Therefore, no IRB approval was required at this stage. However, we plan to use this algorithm to conduct a future single-center prospective trial involving NCCU adult patients during 12 months. The primary outcomes will

be: (1) time to reversal of tissue hypoperfusion, estimated through CRT and serum lactate levels; (2) CPP; (3) organ dysfunction (SOFA score); (4) Glasgow Coma Scale (GCS); and (5) 30-day all-cause mortality. Therefore, we will expect to report those clinical results with patients involved in a forthcoming publication as a prospective study.

Rationale Approach for Thresholds

To develop this conceptual algorithm, the selection of various thresholds of hemodynamic and neurocritical parameters were based on many studies from the medical literature. In turn, we used the resuscitation goals suggested by international guidelines, such as: CRT < 3 s and serum lactate < 2 mmol/L [17, 25]. Additionally, we enumerated various neurocritical parameters that should be maintained to attempt to prevent secondary brain injury [21–23]. Thus, among these parameters we may suggest and enumerate as examples: (1) liberal thresholds for red blood cell transfusion (Hb < 9 g/dl) [21]; (2) adequate oxygenation goals such as PaO₂: 80–120 mm Hg, and SpO₂ > 95% [22], thus avoiding both hypoxia and hyperoxia; and (3) ICP < 22 mm Hg [11] to avoid IH. In addition, to improve the components of the systolic volume while assessing the fluid responsiveness, we may include different methods appropriate for different scenarios, namely: the end-expiratory-occlusion change–velocity time integral (LVOT–VTI) greater or equal to 13% [26] and the pulse pressure variation with a cutoff value higher than 12% [27].

Accordingly, as we discussed previously, maintaining an adequate MAP is pivotal to achieving an adequate CPP. In turn, the initial target of MAP suggested is > 80 mm Hg based on international guidelines for sTBI [28]. Further augmentation to achieve higher thresholds of MAP may be performed depending on the scenario, as noted in the algorithm; for instance, in patients with aSAH caused by a ruptured aneurysm already secured with associated vasospasm. This severe complication, diagnosed by TCD or perfusion computed tomography (CT), requires not only intra-arterial infusions in combination with angioplasty techniques, but also induced hypertension until improvement of neurological deficits, up to 130 mm Hg [29]. In addition, in accordance with international guidelines, discontinuation of nimodipine, which prevents delayed cerebral ischemia in aSAH, may not be necessary in the scenario of nimodipine-induced hypotension [15].

As a final point, the CPP threshold warrants special consideration compared with the preceding steps. Therefore, instead of a fixed cutoff for all neurocritically ill patients included in this algorithm, we suggest aiming for two distinctive ranges of target CPP depending

on the CA status (60–70 vs. 70–80 mm Hg), on the basis of medical literature, which raises the possibility that patients with preserved CA could benefit from higher CPP values [13].

Conclusions

(1) Although newer trials that studied EGDT have not shown improved outcomes compared with usual care, we still encourage the use of these therapeutic algorithms to guide hemodynamic resuscitation in SS, since it could be challenging without a systematic approach. Therefore, (2) to enhance neuroprotection and achieve a better hemodynamic outcome, we propose adding individualized MAP objectives depending on the neurocritical disease and the CA status to the mentioned goals. However, without patient involvement, it is still only a conceptual framework, and its clinical analysis will be addressed in an ongoing future study.

Limitations

The authors recognize that the algorithm presented constitutes a theoretical piece that lacks clinical data or patient involvement to establish that it may be more functional or superior to other algorithms proposed in the literature. In turn, its applicability, comparative performance, or potential superiority over existing algorithms cannot be established at this stage. Therefore, its clinical validation is ongoing, and further robust clinical analysis will be addressed in the future.

Abbreviations

aSAH: Aneurysmal subarachnoid hemorrhage; CPP: Cerebral perfusion pressure; CRT: Capillary refill time; CXR: Chest X-ray; DO₂: Oxygen delivery; EGDT: Early goal-directed therapy; EVD: External ventricular drainage; ICH: Intracerebral hemorrhage; ICP: Intracranial pressure; IH: Intracranial hypertension; HR: Heart rate; IP: Intraparenchymal; LVOT–VTI: Left ventricular outflow tract velocity time integral; MAP: Mean arterial pressure; MCA: Middle cerebral artery; NCCU: Neurointensive care unit; RCTs: Primary randomized controlled trials; SOFA: Sequential organ failure assessment; SS: Septic shock; TCD: Transcranial Doppler; TIC: Thrombolysis in Cerebral Infarction Score; sTBI: Severe traumatic brain injury; VO₂: Oxygen consumption.

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Author Contributions

All the authors meet the same authorship criteria, contributed to the conceptualization, participated in drafting and critical revision, and approved the final version of this manuscript. MR and FZ contributed equally as first authors. WV: Supervision.

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Declarations

Conflict of interest

The author of this article reports no conflict of interest.

Ethical Approval

Not applicable.

Use of Artificial Intelligence (AI)-Assisted Technology for Manuscript Preparation

The author confirms that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript.

Comment

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